In the claims:

Please amend claims 6 and 29 as follows:

6. (Amended) A method of treating or preventing thrombosis in a subject diagnosed as suffering from thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject.

29. (Amended) A method of decreasing plasma fibrinogen in a subject diagnosed as suffering from thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject.

REMARKS

Claims 6, 8-10, 12-15, 29-32 and 34-37 are pending and under examination in the subject application. Claims 6 and 29 have been amended, and no claim has been added or canceled. Accordingly, claims 6, 8-10, 12-15, 29-32 and 34-37 are still pending and under examination.

Applicants annex hereto as Exhibit A a marked-up version of the amended claims to show the changes made herein relative to the previous version thereof.

In the December 17, 2002 Advisory Action, the Examiner maintained the rejections set forth in the April 23, 2002 Final Office Action, as confirmed telephonically by the Examiner in a May 19, 2003 message to applicants' undersigned attorney Alan J. Morrison, Esq.

In response to the Examiner's remarks in the Advisory Action, applicants incorporate herein by reference their remarks set forth in the September 23, 2002 Communication as applicable, and make the following additional remarks to underscore their position that the claimed invention is patentable.

In view of the arguments set forth below, applicants maintain that the Examiner's outstanding rejections have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides methods of treating or preventing thrombosis, and decreasing plasma fibrinogen. These methods comprise administering a tumor necrosis factor antagonist to a subject *diagnosed as suffering from* thrombosis.

This invention is based on applicants' *surprising discovery* that inhibiting the biological activity of TNFα reduces fibrinogen levels in subjects suffering from or at risk of thrombosis. Since fibrinogen plays an integral role in forming thrombi, this invention has considerable use for treating and preventing thrombosis in subjects *diagnosed as suffering from* this disorder.

Rejection Under 35 U.S.C. §102(a)

The Examiner maintained the rejection of claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 under 35 U.S.C. §102(a) as allegedly anticipated by Hommes, et al. (Gastroenterology, 1995, Vol. 108,

No. 4, suppl., p. A838) as "evidenced" by Leardi, et al. (Italian Journal of Surgical Sciences, 1983, Vol. 13, pp. 197-201) and Le, et al. (U.S. Patent No. 5,919,452).

In response to the Examiner's rejection, applicants respectfully traverse.

Briefly, claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 provide methods of treating or preventing thrombosis and decreasing plasma fibrinogen in a subject *diagnosed as suffering from* thrombosis. These methods comprise administering to the subject a therapeutically effective amount of a TNF antagonist.

To anticipate the claimed method, Hommes, et al. would have to teach each and every element thereof, specifically, treatment and prophylaxis in a subject diagnosed as suffering from thrombosis. They fail to do this.

As stated previously, Hommes, et al. teach that the treatment of *Crohn's disease* patients with chimeric monoclonal antibody cA2 decreases "thrombin generation" and "endothelial activation-markers". Hommes, et al. do not teach the treatment or prevention of thrombosis, nor do they teach a decrease of plasma fibrinogen levels. The inability of Leardi, et al. and Le, et al. to cure this deficiency is detailed in applicants' earlier communications.

For these reasons, Hommes, et al., as "evidenced" by Leardi, et al. and Le, et al., fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 satisfy the requirements of 35 U.S.C. §102(a).

Rejection Under 35 U.S.C. §102(b)

The Examiner also maintained the rejection of claims 6 and 8 under 35 U.S.C. §102(b) as allegedly anticipated by Arii, et al. (Circulation, 1994, Vol. 90, No. 4, part 2, p. I522, abstract No. 2811), Vertrees, et al. (ASAIO Journal, 1994, Vol. 40, pp. M554-M559), or Wakefield, et al. (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pp. 258-268).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that each of the above cited references fails to teach each and every element of the rejected claims.

The rejected claims are discussed above.

Arii, et al. provide data suggesting that TNF may induce myocardial slippage after myocardial infarction. However, Arii, et al. do not teach a method of treating or preventing *any* disorder in a subject, and in particular, do not teach the treatment or prevention of thrombosis. Indeed, nowhere do Arii, et al. mention the term thrombosis. In no way can such a reference be deemed to disclose a method of preventing thrombosis in a subject *diagnosed as having* thrombosis.

Similarly, each of Vertrees, et al. and Wakefield, et al., discussed previously, fail to teach a method of treating or

preventing thrombosis in a subject *diagnosed as suffering from* thrombosis.

Therefore, Arii, et al., Vertrees, et al. and Wakefield, et al. all fail to teach each and every element of the rejected claims.

In view of the above remarks, applicants maintain that claims 6 and 8 satisfy the requirements of 35 U.S.C. §102(b).

Rejections Under 35 U.S.C. §103(a)

The Examiner also maintained the rejection of claims 6, 8, 9, 29, 30 and 31 under 35 U.S.C. §103(a) as allegedly unpatentable over Hommes, et al. as "evidenced" by Leardi, et al. and Le, et al. in view of Dhainaut, et al. (Critical Care Medicine, 1995, Vol. 13, pp. 197-201).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Again, claims 6, 8 and 9 provide a method of treating or preventing thrombosis. Claims 29, 30 and 31 provide a method of decreasing plasma fibrinogen. The methods of claims 6, 8, 9, 29, 30 and 31 comprise administering a TNF antagonist to a subject *diagnosed as suffering from* thrombosis. The TNF antagonist can be an anti-TNF antibody or antigen-binding fragment thereof.

The methods of this invention are based on the surprising discovery that inhibiting the biological activity of TNFα reduces fibrinogen

levels in subjects suffering from or at risk of thrombosis. Since fibrinogen plays an integral role in forming thrombi, this invention has considerable use for treating and preventing thrombosis in subjects diagnosed as suffering from this disorder.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at the time of the invention. Third, there must be a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, the teachings of Hommes, et al., as evidenced by Leardi, et al. and Le, et al. in view of Dhainaut, et al., would have to teach or suggest every element of the claims, which they do not do.

Again, Hommes, et al. do not teach the treatment or prevention of thrombosis, or a decrease of plasma fibrinogen levels, nor do they mention the terms "thrombosis" and "plasma fibrinogen". Moreover, Hommes does not teach or suggest the treatment of a subject *diagnosed as suffering from* thrombosis.

Combining Hommes, et al. with Dhainaut, et al. does not cure this deficiency. Dhainaut, et al. teach the use of an anti-TNF antibody in the treatment of *septic shock*. Dhainaut, et al. do not teach treatment or prevention of thrombosis, or the decrease of elevated

fibrinogen levels.

Moreover, these references, when combined, would also have to motivate one of ordinary skill to combine their teachings at the time of the invention. Absent a teaching of all elements of the claimed invention, one of ordinary skill would also have no motive to combine or reasonable expectation of success.

Applicants' invention is based on the surprising discovery that inhibiting TNFα activity reduces fibrinogen levels in subjects diagonsed as suffering from or at risk of suffering from thrombosis. At the time of this application, this finding was unknown to those skilled in the art. Applicants reassert that by ignoring this fact, the Examiner makes an impermissible leap by asserting that the "successful" use of TNF antagonists against Crohn's disease and sepsis/septic shock is predictive of success against the wholly distinct disease of thrombosis.

In light of these teachings and their shortcomings, the Examiner has failed to show that the cited references teach or suggest every element of the claims, or create a motive to combine or expectation of success. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 9, 29, 30 and 31 over Hommes, et al. as "evidenced" by Leardi, et al. and Le, et al. in view of Dhainaut, et al.

The Examiner also maintained the rejection of claims 6 and 8 under 35 U.S.C. §103(a) as allegedly unpatentable over Fisher, et al.

(Critical Care Medicine, 1993, Vol. 21, pp. 318-327) in view of Hooper, et al. (Blood, 1994, Vol. 84, pp. 483-489) or Jolin, et al. (Acta Anaesthesiologica Scandinavica, Supplementum, 1991, Vol. 95, pp. 40-52).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The rejected claims are discussed above.

Fisher, et al., in view of Hooper, et al. or Jolin, et al., fail to teach or suggest every element of the claims.

Fisher, et al. teach essentially what Dhainaut, et al. teach, i.e., the use of an anti-TNF antibody in the treatment of *sepsis*. Fisher, et al. do not teach treatment or prevention of thrombosis, the decrease of elevated fibrinogen levels, or the treatment of a subject *diagnosed as having* thrombosis.

Again, as stated above, the mere use of TNF antagonists for the treatment or prevention of diseases generally, and sepsis/septic shock specifically, does not suggest or motivate one to use TNF antagonists in the treatment or prevention of thrombosis or elevated fibrinogen levels.

Hooper, et al. do not cure this defect. Hooper et al. teach that treatment with anti-TNFα antibodies can, via an as yet unknown mechanism, reverse the inhibitory effect of TNF on protein S levels. Hooper, et al. offer no data or other evidence that anti-

TNFα antibody treatment reduces or prevents thrombosis. Indeed, Hooper, et al. acknowledge that the correlation between protein S deficiency and thrombosis is "not well documented."

Jolin, et al. also do not cure the deficiencies of Fisher, et al. because they do not teach the treatment or prevention of thrombosis. Jolin, et al. do teach methods aimed at reducing hypoxic pulmonary vasoconstriction (HPV) in the treatment of adult respiratory distress syndrome (ARDS). ARDS is a syndrome with which a myriad of diseases may be associated. As such, a large number of different ARDS mediators and vasoconstrictive agents were examined for their potential for inhibiting HPV. The Examiner has not demonstrated that *any* of these are classified as TNF antagonists. Jolin, et al. also disclose that, at the time of their study, there existed *no* exact information about the effects of HPV on coagulation factors. In fact, they do not even mention thrombosis.

In light of these teachings and their shortcomings, the Examiner has failed to show that the cited references teach or suggest every element of the claims, or create a motive to combine or expectation of success. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6 and 8 over Fisher, et al. in view of Hooper, et al. or Jolin, et al.

The Examiner also maintained the rejection of claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Le, et al. (U.S. Patent No. 5,656,272) in view of

Hooper, et al. or Jolin, et al.

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The references and rejected claims are discussed above.

Le, et al. in view of Hooper, et al. or Jolin, et al. fail to teach or suggest every element of the claims. Le, et al. teach the treatment of Crohn's disease with chimeric monoclonal antibody cA2 and antibodies which compete therewith. Le, et al. do *not* teach the use of these antibodies to treat or prevent thrombosis (especially in a subject diagnosed as having same), or to decrease plasma fibrinogen levels. Neither Hooper, et al. nor Jolin, et al. cure this defect for the reasons discussed above. Likewise, these references also fail to create a motive to combine or a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 10, 12-15, 29, 30, 32 and 34-37 over Le, et al. in view of Hooper, et al. or Jolin, et al.

In view of the above remarks, applicants maintain that claims 6, 8-10, 12-15, 29-32 and 34-37 satisfy the requirements of 35 U.S.C. §103(a).

Summary

In view of the remarks made herein, applicants maintain that the

claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $2,730.00 sum, is deemed necessary in connection with the filing of this Preliminary Amendment and accompanying RCE. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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Marked-Up Version of Claims

6. (Amended) A method of treating or preventing thrombosis in a subject diagnosed as suffering from [or at risk of] thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject.

29. (Amended) A method of decreasing plasma fibrinogen in a subject diagnosed as suffering from [or at risk of] thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject.